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Letter to the Editor

Natural Family Planning and Down Syndrome—Matching and Confounding in a Case Control Study

To the Editor:

A case-control study of Castilla et al. [1995] published in the Journal was conducted to determine the association between Down syndrome and the use of natural family planning (NFP). This powerful study design has an enhanced potential for sample distortion and is particularly prone to error and bias.

The authors report collecting data on more than 5,000 case-control pairs, and they provide data on 4,925 mothers of malformed infants (6.6% NFP users: the number has to be 327 instead of 227 in the text), and on 4,802 mothers of controls (6.0% NFP users).

For this source population the authors do not: 1) define their exposure category, i.e., who is an NFP user (how many cycles, just one, life-long?); 2) explain why they provide these data on malformed children, when the objective of their study is trisomy 21; 3) state why they present data on <5,000 pairs; or 4) explain why the numbers of cases and controls are different; they should be the same according to the short outline of the study design. Castilla et al. [1995] continue to analyze data on their study population: 476 mothers of babies with Down syndrome (cases) and matched controls. Furthermore, 5) they omit stating their matching factor(s), and from their design (data existing for a large source population) there seems to exist no reason for matching at all. Confounding can be controlled in the analysis, and efficiency is not at issue. Also, 6) they leave it up to the reader to calculate that from 199 discordant pairs (for NFP use), there were 121 cases who were NFP users, while their matched controls were not, and that 78 controls were NFP users while their matched cases were not (these figures were calculated from the OR, assuming that the authors used the 2×2 table "as usual" (e.g., Schlesselman [1982]). Assuming these calculations are correct and given that there were no matched pairs for which controls as well as cases were NFP users, the frequency of NFP users is minimally 25.4% (121/476) for cases and 16.4% (78/476) for controls, respectively. The authors do not comment on these striking frequencies if one compares them with the 6.3% (614/9,727) in the source population. In case-control studies, matching on factors associated with exposure builds confounding into the data, whether or not there was confounding initially in the source population. The confounding created by matching in a case-control study is generally a bias towards the null value of the effect, leading to an underestimation of the OR. If the matching factor was uncorrelated with exposure, then matching would not influence the exposure distribution of the controls, but if the correlation were zero, the matching factor is not a confounder, since a confounding factor must be associated with the exposure as well as with the effect. The confounding created by matching in a case-control study requires control of confounding by the matching factor in the analysis. Lastly, 7) they write about "odds ratio 95% confidence intervals (OR) = 1.55" and then give a chi-square value, and 8) they do not justify a beta of 0.8; if they want to show that exposure and outcome are not associated to a clinically important degree, the probability of failing to detect the degree of association should be very low (e.g., beta 0.9).

I think that the reporting of a case-control study and of data on the Latin-American Collaborative Study of Congenital Malformations (ECLAMC) deserves more care and a proper analysis to be of any use for the readership of the Journal.

REFERENCES

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